198-Plat
Efficient Dynamic Protonation and Constant pH Simulations with Explicit Solvent: Calculation of Apparent pKa Values in Proteins
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The pKa's of the ionizable amino acids are crucial for the function of many proteins as they are key factors that determine their electrostatic potential and its spatial distribution, often controlling and optimizing enzymatic catalysis. Further, during conformational motions pKa's and protonation states particularly of histidines may change. In established force field simulation, however, this effect is typically not included, and protonation states must therefore be either guessed or derived from experiment. There have been a number of approaches to include protonation effects within simulations, mainly based on continuum electrostatics or implicit solvent molecular dynamics [1–3].
However, these methods lack the effect of the hydrogen bonding and the entropy contribution that comes from the solvent. Here we present the implementation and application of a dynamic protonation atomistic simulation method with explicit solvent, which also allows for explicit solvent constant pH MD simulations, previously developed also in our group [4]. This method is used here to calculate the pKa's of the ionzable groups in proteins. In order to validate it, we selected a number of prototypic proteins and calculated titration curves and pKa values from constant pH simulations at a range of different pH values.
The results compare favorably with measured values, and explain atomistically the strong deviations of some of the calculated pKa values from the solution ones.
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pH Replica-Exchange Method Based on Discrete Protonation States
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We propose a new algorithm for obtaining proton titration curves of ionizable residues. The algorithm is a pH replica-exchange method (PHREM), which is based on the constant pH algorithm of Mongan et al. (J Comput Chem 2004;25:2038-2048). In the original replica-exchange method, simulations of different replicas are performed at different temperatures, and the temperatures are exchanged between the replicas. In our PHREM, simulations of different replicas are performed at different pH values, and the pHs are exchanged between the replicas. The PHREM was applied to a blocked amino acid and to two protein systems (snake cardiotoxin and turkey ovomucoid third domain), in conjunction with a generalized Born implicit solvent. The performance and accuracy of this algorithm and the original constant pH method (PHMD) were compared. For a single set of simulations at different pHs, the use of PHREM yields more accurate Hill coefficients of titratable residues. By performing multiple sets of constant pH simulations started with different initial states, the accuracy of predicted pKa values and Hill coefficients obtained with PHREM and PHMD methods becomes comparable. However, the PHREM algorithm exhibits better samplings of the protonation states of titratable residues and less scatter of the titration points and thus better precision of measured pKa values and Hill coefficients. In addition, PHREM exhibits faster convergence of individual simulations than the original constant pH algorithm.

200-Plat
Aggregated yet Disordered: A Molecular Simulation Study of the Self-Aggregation of Elastin
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Elastin is the protein responsible for the elastic recoil of skin, arteries, and lungs. Elastin exhibits high resilience and remarkable durability; it also undergoes phase separation and self-organization into a fibrillar structure upon increasing temperature. These properties make elastin ideal for biomaterials applications. In order to investigate the molecular basis for elastin self-aggregation, we performed extensive atomistic molecular dynamics simulations of a monomer and an aggregate of eight elastin-like peptides in explicit water. These simulations required a total time of nearly 0.5 ms, and utilized simulated tempering distributed replica sampling, a method that relies on a random walk in temperature to enhance conformational sampling. We obtain a configurational ensemble of the elastin-like aggregate that resembles a ''polymer melt'' in which the chains are completely entangled with each other, but retain significant hydration and do not form a water-excluding hydrophobic core. Within the aggregate, the chains act to ''solvate'' each other: intramolecular interactions present in the monomer in aqueous solution are largely replaced by intermolecular interactions in the aggregate. As a result, the overall chain dimensions are similar to the expected dimensions of chains in an ideal solvent, a state in which chain entropy is maximized. This is the prediction of the Flory theorem for generic polymer chains within a polymer melt, but has never, to our knowledge, been observed before for an aggregate of polypeptide chains in atomistic detail. Finally, we note that our results are not consistent with the current model of elastin self-aggregation, which involves a conformational transition of a monomer towards a more ''ordered'' aggregation-prone state. Instead, we propose a model in which both the hydrophobic effect and the enhanced chain entropy afforded by the interactions with other peptides within the aggregate favour elastin self-aggregation.

201-Plat
A Multisite Ion Model that Improves Free Energy Calculations in Molecular Dynamics Simulations
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Current ion models in molecular mechanics are simple spheres, and their interactions are solely determined from the radius of the sphere and the total charge. This set of parameters is chosen to closely reproduce the hydration free energy for the ion, but this exercise uses all the available degrees of freedom and our ability to reproduce the binding free energy to a protein or other thermodynamic quantities is therefore limited. Here we introduce a new model where we distribute the total charge of the ion into n-dummy centers that are placed in the direction of the coordinating atoms. We have parameterized this model for two divalent cations, Ca2+ and Mg2+, and have tested the model's accuracy in a variety of simulations. With this model we are not only able to correctly predict the free energy and selectivity for cation binding sites, but we achieve better coordination geometries and can capture more subtle effects such as the exchange of inner shell waters. One further advantage of this model is that it does not use higher-order electrostatics and thus can be easily used with standard force fields.

202-Plat
Non-Equilibrium Free Energy Calculations for Ligand Optimization
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Computational methods for rational drug design rely on the estimation of the free energy differences upon a ligand binding to the target biomolecule. Molecular dynamics based alchemical free energy calculations provide a powerful method allowing accurate estimations of relative binding affinities. The alchemical approach requires exploitation of nonphysical pathways over thermodynamic cycles: atoms in the system may be created, morphed or annihilated. A modified form of the soft-cored non-bonded interaction potential is needed for such alchemical transitions when applying the Crooks Fluctuation Theorem. We propose a new soft-core potential suitable for fast non-equilibrium transitions. The new construction of the potential function prevents singularities and additional local minima that may lead to inaccurate estimations of the free energies. We further employ the scheme of thermodynamic integration in combination with the non-equilibrium transitions based on the new soft-core potential to address the problem of lead optimization.

Workshop: Optogenetics: Development of Novel Optical Tools for Controlling Protein Cellular Behavior

203-Wkshp
Biophysical Studies of Natural Photoreceptors: Application to Optogenetic Tool Optimization
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